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"Immunological Surveillance"

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Introduction:

Immunological surveillance is the term used to describe part of the immune system's general function of recognising and destroying foreign protein and polysaccharide when the foreign substance is derived from what were normal body cells. These cells can be altered by a variety of factors uncluding somatic mutation, chemicals, viruses and irradiation, agents classically associated with carcinogenesis. In fact the idea of immunological surveillance really arose from consideration of some of the immune phenomena associated with clinical and experimental tumors.

The evidence includes tumor histology with lymphocyte and plasma cell infiltration; the demonstration of tumor immunity and tumor specific antigens; experimental work on neonatal and adult mice in tumor induction; statistical analyses of tumor incidence in cases of immunological disorders and the success of therapeutic means aimed at augmenting the destruction and recognition sides of the system.

I have approached the presentation of this evidence in terms of what one would theoretically expect the properties of the system to be for it to be valid.

The great attraction of the concept is that it provides a stimulating and fresh outlook on the problem of CANCER, suggesting various experiments which modern developments in technique and equipment

will allow for the first time. Its appeal to the clinician is its immunological basis with the resurrection of Almroth Wright and his early 1900's belief that immunotherapy aiding the body's own defences would be the means of curing all ills.

The concept has taken shape in the last twenty years. Therapeutic possibilities suggested by it have been tried out on animals. Some considered the results encouraging enough to attempt the same in man. Their successes and failures I shall describe and discuss in a later section of this essay.

Immunological surveillance is thought of as the latest development in the evolution of adaptive immunity. Invertebrates lack antibody production or any of the other characteristic features of the mammalian immune system. However they do have a protective response against the entry of foreign organisms or material through phagocytic cells. Primitive vertebrates e.g. hagfish are very similar to the invertebrates but the lamprey can produce limited antibodies, has a primitive thymus and will reject homografts. All the higher fishes show immune responses which are much more specific. Amphibia and reptiles are similar. The increase in body temperature increases the speed and effectiveness of the immune responses.

The stimulus to the development of a surveillance mechanism is thought to be that increase in animal size and length of survival meant

an increased risk of somatogenetic changes in cells and hence an increased risk of aberrant cells developing. I shall describe in detail the cellular system which evolved to meet this challenge.

CONCEPT:-

Immunological surveillance is a term used to describe the state of affairs in which aberrant cells possessing a foreign antigen induced by radiation, mutation, viruses or chemicals, may evoke a homograft type reaction with resulting destruction. It is particularly applied to tumor cells in which a breakdown of this system allows an abnormal clone of cells with a selective advantage over other cells to develop.

BASIC IMMUNOLOGICAL PROBLEMS of the concept are many

(1) The recognition problem -

- (a) What are the cells involved? : lymphocyte and macrophage
- (b) How do these cells recognise
and respond to antigen? : surface antibody (Ab)
- (c) Do tumor cells have new
antigens? : Yes (some do)

(2) The destruction process -

- (a) What are the consequences lymphocyte proliferation
of lymphocyte interaction : and tumor cell destruc-
with tumor cell antigen (Ag) tion.

(b) The interactions of lymphocyte
and macrophage in destruction
of tumor cells

(c) The part played by cytotoxic
Ab in destruction : - little

Why do tumors survive? : logically a failure of any element of the
recognition or destruction system.

- also the concept of 'tolerance'.

Epidemiological evidence pertaining to immunosurveillance in man.

Therapeutic possibilities and : (1) Improve recognition
procedures carried out to date (2) Improve destruction

THE RECOGNITION PROCESS

(a) The cells involved:

The theory of immunological surveillance requires a highly efficient and sensitive recognition system. At present it is believed that the lymphocytic and to a lesser extent the macrophage cell systems represent a cellular component of such a system.

Lymphocytes vary both morphologically and functionally. Large lymphocytes are actively dividing lymphocytes of uncertain origin which are often found in the stroma of the villi of the small intestine. They can resemble immature plasma cells or divide to give rise to small lymphocytes. They resemble small lymphocytes in the early stages after stimulation by antigens to undergo transformation.

Small lymphocytes are identical under the light microscope but vary in life cycle and function and origin.

Long-lived lymphocytes are derived from a stem cell in bone marrow which populates the lymphoid tissue of the gut and associated structures and the thymus. In the thymus these stem cells differentiate to lymphocyte precursors which divide to give rise to small lymphocytes. Some of these small lymphocytes leave the thymus and populate the gut associated lymphatic tissue, especially the paracortical zones of lymph nodes and around the central artery of the Malpighian bodies of

the spleen. The lymphocytes in these areas neither die or divide but circulate freely in the blood stream. These thymic lymphocytes produce the cell mediated immune reaction which destroys tumor cells as well as playing a part in the recognition system.

Short-lived small lymphocytes are thought to arise from the bone marrow cells which populate the gut associated lymphatic tissue directly. It is thought they are the progenitors of lymphocytes which are in turn the precursors of antibody - forming cells found in the medulla of lymph nodes and spleen.

In summary - the lymphocytes involved in the recognition part of immunological surveillance are long lived uncommitted lymphocytes derived from the thymus. They are sometimes known as immunocytes - cells of one genetic capacity which will form clones when they meet up with the appropriate antigen.

The macrophage system is made up of cells differing morphologically and functionally. They phagocytose particulate material in the circulation including antigen. Soluble antigen they engulf by pinocytosis. Macrophages are found in many tissues but especially liver, lung, spleen and lymph nodes. Some are tissue fixed probably derived from precursor cells in the tissue, while others are actively motile and found in the blood. Those of importance in the recognition

of tumor cell antigens are found alongside lymphocytes in the gut associated lymphoid tissue and in the thymus.

How do these cells recognise and respond to antigen? :

The thymic long-lived small lymphocyte (immunocyte) is capable of producing at the most three different antibodies by genetic limitation. Samples of these antibodies are to be found bound to the surface of the immunocyte. Thus when the specific antigen comes into contact with this immunocyte Ag - Ab binding will take place. The immunocyte responds by blast transformation replicating itself and thus increasing the recognition of similar antigens on other adjacent cells. However the question arises - does the immunocyte go to the antigen or does the antigen come to the immunocyte. This problem has theoretical implications concerning tumor survival and will be discussed in a later section.

The macrophage also has antibody on its cell surface, taken up passively as it has a function catabolising antibody. Thus it is capable of fixing antigen which is itself structural e.g. part of a cell wall. Blood macrophages unlike lymphocytes are freely motile cells capable of passing through capillary membranes into the tissues. They are therefore theoretically capable of recognising cell fixed

antigen outwith the blood stream and free antigen in the blood stream. The macrophage response is thought to be formation of an MRNA complex with antigen which can act on lymphocytes causing them to divide, become cytopathic and destroy the antigen or cell it is part of. Surface fixed antigen can also act as a long term stimulus to antibody formation by lymphocytes in the medulla of lymph nodes.

The importance of these cells to modern evaluation of a tumor's pathogenicity and the patient's prognosis is great. Often there are considerable differences in the extent to which there is a round-celled reaction at the edge of the tumor mass. Often plasma cells are conspicuous among lymphocytes and macrophages. Two studies to correlate the intensity of round-celled response with survival showed a ^{direct} ~~inverse~~ correlation.

Do tumor cells have new antigens?

There have been two approaches to answering this question. The first entailed showing that there was a gross immune response against tumor cells, the assumption being made that as the body's immune system does not react against the host's tissues any evidence of an immune reaction would be due to new tumor specific antigens.

The methods used included prior immunisation by

- (a) transplanting a tumor from one animal to another ^{of an inbred strain} and removing it surgically after it had reached a certain size.
- (b) injecting irradiated tumor cells which are still metabolising normally but are incapable of division.
- (c) 'immunising' an animal with a dose of tumor cells too low to cause a tumor.

That immunity is produced by these means is shown by the evidence that when these animals are then subject to a dose of tumor cells sufficient to cause a tumor, the cells are destroyed whereas a similar dose in unimmunised animals causes a tumor in every case.

It was believed at first that tumor cells were de-differentiated cells which had lost antigens and this was shown experimentally but gradually evidence for the formation of 'new' antigens accrued.

Chemical carcinogens producing different tumors in the same animal species were shown to produce different antigens in each tumor while viral induced tumors though structurally different were found to have the same viral specific antigen. Chemically induced tumors tend to differ very widely in their immunising capacities.

The second approach utilised the tools of diagnostic serology and as such was more applicable to man. Virtually all the work described above refers to animal experimental tumors. Evidence for tumor antigens in man includes the following -

(1) Indirect evidence through complement fixation tests detecting antibody to a tumor suspension acting as antigen. (However the possibility of antibody being made in response to infection and necrosis of tumor cells still exists). Graham^eGraham tested the sera of 48 cancer patients (tumor types unknown to me) in this way and got titres of 1 in 16 to 1 in 128 with the most advanced cases lacking circulating antibody.

(2) Antibody reactions were also elicited by the following procedures -

- (a) irradiation or intra muscular injection of whole tumor antigen with adjuvant (Finney, Byers and Wilson) in twelve out of fourteen patients with a wide variety of tumors.
- (b) Greensham, Brown and Schwartz showed that extracts of

tissues from human leukaemias and Hodgkin's disease injected into man gave an antibody response not induced by similar extracts from non-leukaemic tissues.

(3) Immunofluorescence has been used to show antibody attached to tumor cells in 30% of cases of malignant melanoma. It has also been shown that there was cross-reactivity between melanoma cells and the sera from a number of different melanoma patients (Muna et al). Thus limited evidence is available for 'new' tumor antigens.

THE DESTRUCTION PROCESS

(a) The parts played by the lymphocyte and macrophage.

The immunoblast is formed by

- (1) Antigen contact with antibody on the small lymphocyte (uncommitted immunocyte) surface.
- (2) Passage of a MRNA - Ag complex from the macrophage.

The immunoblast divides to form a clone of cytotoxic committed immunocytes which are capable of destroying the cell whose Ag they are committed against and a clone of plasma cells which can produce antibody. (Whether this Ab is cytotoxic or not is often unknown).

The dendritic macrophages and lymphocytes inter-react in a complicated manner to achieve the formation of these cell populations.

As more is known about this destruction process and because of its possible manipulation for therapeutic purposes I shall describe it at some length.

The process is similar to delayed type hypersensitivity -

In SUMMARY (1) lymphocytes and macrophages are effectors of the reaction and affected by it.

- (2) Sensitisation to an antigen can be transferred by whole lymphocytes and macrophages or TRANSFER FACTOR (? the MRNA - Ag complex mentioned previously).

- (3) Transfer factor causes lymphocytes to secrete many other protein factors.
- (4) Sensitised lymphocytes will transform in antigen presence to produce more lymphocytes and also acquire the capacity to kill by contact.
- (5) The role of the macrophage though less clear appears to be
 - (1) to initiate transfer factor formation
 - (2) to initiate antibody formation by the lymphocyte
 - (3) to be subject to an antibody feed back which inhibits them and can thus diminish the destruction process.

Antigen activation of sensitised lymphocytes results in the synthesis and release by these cells of soluble cell-free factors. They are called LYMPHOKINES and include

- (1) pyrogen : responsible for the immune 'fever' of many conditions
- (2) macrophage inhibiting factor (MIH) : localises macrophages at the site of the reaction.
- (3) mitogenic factor (MF) : stimulates non-sensitised recipient lymphocytes to transform. This will increase the size of the cytotoxic reaction but may result in

the destruction of nearby cells which lack the initiating antigen.

(4) cytopathic factor (CF : lymphotoxin) : this substance has been shown to be cytotoxic for mouse fibroblasts in monolayer culture. It may also increase the permeability of blood vessels in the area to mononuclear cells by destroying vascular endothelium, thus amplifying the immunological reaction.

(5) chemotactic factor (ChF) : again amplification of the response.

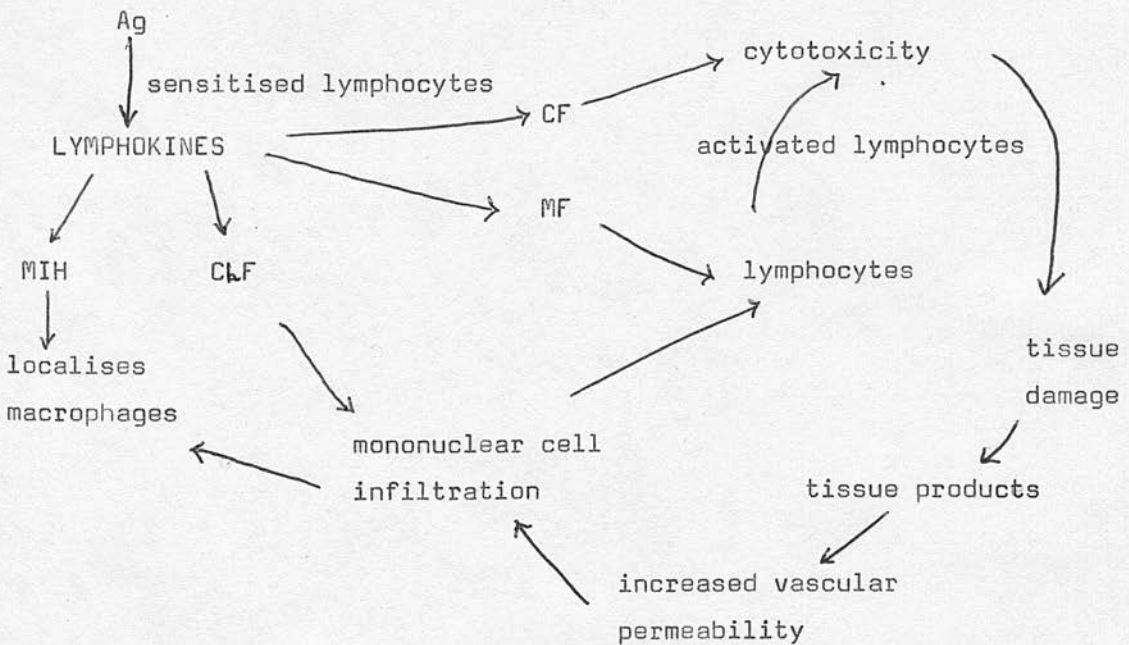
These factors are of molecular weight 80-50,000, protein, and act independently of antigen; classical antibody and antigen - antibody complexes (Dumonde et al 1969). Other factors which have been described as being released in identical experimental models are a material which is chemotactic for monocytes (Ward & David 1969) and a material which promotes macrophage phagocytosis (Barnet, Pekarek & Johanovsky 1968).

Antigen activation of sensitised lymphocytes also gives these lymphocytes the capacity to kill specific target cells on contact. They alter the osmotic equilibrium of these cells, which swell and burst.

Antigen affects MACROPHAGES by

- (1) initiating transfer factor secretion : lymphokines produced
- (2) increasing intracellular killing
- (3) in a secondary manner, via lymphocytes and macrophage inhibiting factor.

These various interactions can be summed up in the following diagram (after PANAYI)



MIH	macrophage inhibiting factor
CLF	chemotactic factor
MF	mitogenic factor
CF	cytopathic factor

An outline such as the above serves to illustrate the key areas in which therapy may theoretically be applied. Applications will be discussed in the therapeutic part of this essay.

The part played by Antibody in destruction -

Antibodies can be cytotoxic or cytophilic, the distinction being related to the capacity to fix complement.

Cytophilic antibodies:

- (1) coat macrophages and allow them to become cytotoxic.
- (2) coat tumor cells and possibly block destruction of these cells by preventing cytopathic lymphocytes from fixing to these cells.

Cytotoxic antibodies can destroy tumor cells in their own right. However their concentration inside solid tumors is much less than their concentration in plasma. It appears that they function best in the elimination of blood metastases from tumors.

Some evidence for these ideas is found in studies done on patients with malignant melanomas.

- (1) Distant metastases were found only in those patients with no antibody.
- (2) Spread is by the local lymphatics if antibody is present in the blood but by the blood only when antibody is absent.

TUMOR GENESIS and SURVIVAL

Tumors can arise

- (1) Spontaneously due to genetic copying errors
- (2) Through extraneous radiation damage
- (3) From chemical carcinogens
- (4) From viruses

That they survive is presumably due to failure of any element of the recognition or destruction system.

- e.g. failure of the recognition system could be due to:
- (1) lack of tumor specific Antigen.
 - (2) failure of macrophage to take up antigen due to
 - (a) no ag. in the system
 - (b) no Ab on macrophage surface
 - (c) Blockade of the system
 - (3) No reciprocal antibody producing uncommitted lymphocytes.
- failure of destruction:
- (1) failure of proliferation i.e. no cytotoxic cells produced
 - (2) failure of access to tumor
 - (3) enhancing antibody hiding tumor specific surface antigen.

The phenomenon of TOLERANCE and its relevance to tumor survival.

Tolerance is the lack of reactivity of the body's immune mechanisms to an antigen. The concept best explaining it is the clonal selection theory of Macfarlane Burnet in which the cells which should respond to a particular antigen have either been inactivated or do not exist.

1. INACTIVATION: this has been shown experimentally to occur in response to very low or very high doses of antigen. There appears to be an intermediate dose range where an immune response is obtained. A tumor of low or very high antigenicity could paralyse the immune system in a similar manner. However often the continued presence of antigen is necessary to prolong tolerance. This would rationalise surgical removal of as much tumor tissue as possible with radio or chemo therapy to destroy residual cells, thus reducing antigen concentration and hopefully reversing tolerance.

Whether surgery by dissemination of large numbers of tumor cells actually induces tolerance is debatable. A tumor of low antigenicity could have its blood antigen concentration brought into the dose response range and thus aid the immune-response. It would appear that most tumors are of this low antigenicity type.

2. Lack of specific cells as the reason for tolerance might occur in the following situations

- (1) following excessive radiation 'treatment'
- (2) following excessive chemotherapy
- (3) following tumors of lymphoid tissue
- (4) because the adult thymus is impermeable to 'self' antigens and no immunocytes to these antigens are produced.

The relevance of tolerance to tumor survival is uncertain because not enough is known of the body's cellular state and the immunology involved.

An alternative approach was that adopted by Hellstrom in which surveillance is regarded as a local phenomenon involving different histocompatibility antigens between adjacent cells and not immunological. However Mintz succeeded in producing an 'allophenic' mouse by embryological manipulation and fusion of early embryos of two distinct histocompatibility types. Mice produced in this way show complete tolerance to and between both types of cell.

EPIDEMIOLOGICAL EVIDENCE PERTAINING TO IMMUNOSURVEILLANCE IN MAN

Medicine and statistics have both reached the sophisticated state of being able to provide evidence pertaining to immunosurveillance in man. The discovery of immunological deficiency diseases involving cell mediated immunity; the operation of thymectomy for thymoma or myasthenia gravis; immunosuppression in some auto immune diseases but also for organ transplantation; and the age distribution of cancer have all been subject to statistical analyses of the consequences. The following evidence has been uncovered.

(1) IMMUNOLOGICAL DEFICIENCY DISEASES -

~~4~~ congenital types

- (1) Ataxia telangiectasia - immunological deficit involves defective cellular immunity and antibody response to antigen; abnormalities in the level of serum immunoglobulin and in the thymus -

200 cases : 14 malignant tumors : 9 of which involved the reticuloendothelial or lymphocytic systems

- (2) Wiskott-Aldrich syndrome - humeral and cellular immunity involved -

90 cases : 11 malignant tumors : mainly reticuloendothelioses



(3) Chediak:Higashi syndrome - precise defect unknown

50 cases : 11 malignant tumors : mainly lymphomas

(4) Agammaglobulinaemia and hypogammaglob^ulinaemia -

high tumor incidence : variety of tumors

In general the tendency has been for a significant increase in tumors in these people but particularly the reticuloendothelioses. However the number of people involved is very low and often the precise nature of the immunological defect has been in doubt.

It has also been suggested that the high incidence of lymphomas and perhaps also of carcinomas in gluten enteropathy and cancers in ulcerative collitis could have an immunological basis if it is accepted that these disorders are auto-immune in origin.

(2) THYMECTOMY :

Agensis in children results in early death from infection. In adults thymectomy is practised for myasthenia gravis and thymoma. The evidence to date on a series of patients (419) with a follow up period of 12.3 years is that the incidence of tumors is normal with a normal distribution of types.

(3) IMMUNOSUPPRESSION -

Therapeutic immunosuppression is a relatively new technique brought to prominence by organ transplantation. It includes

- (1) drugs (azathioprine and prednisolone)
- (2) antilymphocytic serum
- (3) splenectomy and thymectomy

Kidney transplantation has revealed

(1) remarkable destruction of tumor, inadvertently transplanted from the donor's kidney, when immunosuppression was removed.

(2) a 50 fold increase in the number of reticuloses in transplant patients receiving antilymphocytic serum.

Of 4000 renal transplant patients 37 neoplasms have arisen, 15 of which have been reticulum cell sarcoma (12) or other lymphomas (3).

It appears that transplant patients will require a far longer follow-up before we can tell whether the incidences of tumors other than the lymphomas is increased.

(4) AGE DISTRIBUTION -

The immune system is thought to be at its weakest at the extremes of life. These times coincide with the highest incidences of tumors, excepting seminoma of the testis and some varieties of Hodgkin's disease in young men and tumors of the uterus in middle aged rather than elderly women. However statistical analyses of age incidences of other diseases of the elderly show similar patterns to cancer.

Possibly all these diseases are manifestations of some process

of ageing albeit even an ^{no}immunobiological process but the data presently available does not allow us to come to any definite conclusions.

In conclusion: derangement of the immune system seems to give an increased incidence only of tumors of the immune system. The lack of data on whether intensive immunosuppression will give an increased incidence of other tumors is critical.

THERAPEUTIC POSSIBILITIES AND PROCEDURES

IMPROVED RECOGNITION - The following possibilities exist.

1. Increase the antigenicity of the tumor

(a) by low level irradiation

(b) by linking other antigens to tumor cells to
increase the degree of recognition

(c) by increasing antigen release : say using lysosomal
enzymes ortrypsin and chymotrypsin

(d) by eliminating enhancing antibody, blocking
recognition and destruction.

(a) Low level irradiation is considered unnecessary when large doses of X-rays will destroy tumor cells more efficiently. However this destruction is not 100% and high doses do affect whatever immune reaction there is.

(b) E. Klein considered he was increasing the antigenicity of a tumor when he applied 2, 3, 5, tri-ethylene iminobenzoquinone to a variety of pre-malignant and malignant skin lesions in man. He achieved resolutions of more than 95% of pre-malignant keratoses, superficial basal cell carcinomas and squamous cell carcinomas in situ in 50 patients without recurrences for observation periods of up to 5 years.

However his studies on neoplasms of NON EPIDERMAL origin showed

- either (1) challenge reaction to T.E.I.B. similar to normal cells
(2) no reaction at all.

These included malignant melanoma, adenocarcinoma of breast, mesothelioma, lymphosarcoma, Hodgkin's and other lymphomas.

His method was to apply the compound to the tumor areas for up to 2 weeks; then to apply the compound over the whole body area. This usually resulted in the rapid destruction not only of visible areas but of unsuspected areas as well. The healing process was unimpaired by this method.

The compound Klein applied probably acted as a hapten and bound to protein on the tumor cell surface, the complex then acting as an antigen. He was eliciting a form of contact hypersensitivity. The lesions he dealt with are all very sensitive to X-rays but his method leaves the healing process unimpaired, a very important consideration in treatment.

(c) The use of proteolytic enzymes to increase antigen release from a tumor is feasible but at present unattempted, even experimentally.

(d) A method of eliminating enhancing antibody without affecting cytotoxic antibody is unknown. If cytotoxic antibody is as unimportant in tumor destruction as at present it appears to be then removal of gamma globulin from the plasma could be attempted. The value of such

a procedure has still to be verified experimentally. However, the part actually played by enhancing antibody is unknown for virtually all tumors; in malignant melanoma it has been shown to play no part.

2. Increasing the number of LYMPHOCYTES for recognition by

- (1) transfusion from an isogeneic donor
- (2) cell culture techniques
- (3) radiation

The first can easily lead to a graft-versus host reaction and lacks specificity. No adequate cell culture techniques have been devised to make the second feasible and the third, radiation, is quantitatively inadequate.

3. Increasing the number of MACROPHAGES for recognition

- (1) BCG injections
- (2) killed corynebacterium parvum
- (3) inducing inflammation around the tumor

Injections of BCG or killed *C. parvum* are non-specific stimulators of the R.E.S. increasing macrophage number. Their use by Mathe in the treatment of leukaemia has been impressive. The macrophages produced probably act both via recognition and destruction processes. I shall describe their use by Mathe under methods of increasing destruction.

Inducing inflammation around a tumor certainly brings macrophages into the vicinity. For skin tumors Gorer found that following infection the tumors sometimes disappeared. In man malignant melanomas

may respond to vaccinia and basal cell carcinomas to painting with dichloronitrobenzene.

IMPROVED DESTRUCTION The following possibilities exist.

- (1) Increasing the number of sensitised lymphocytes
- (2) Increasing the number of sensitised macrophages
- (3) Increasing the amount of cytotoxic antibody
- (4) By employing other immunological phenomena such as
 - (a) florid delayed type hypersensitivity
 - (b) graft v. host reactions

1. Increasing the number of sensitised lymphocytes

(a) This can be done by injecting tumor cells into the site of drainage of unaffected lymph nodes elsewhere in the body. The pyroninophilic blast cells will appear in the lymph draining the lymph node between four and ten days after antigenic stimulation.

(b) Experiments have shown that cytotoxic lymphocytes can be obtained by mixing circulating small lymphocytes with tumor cells in vitro. Cell separation can be done using the IBM continuous Blood Cell Separator. Presumably there are relatively high levels of circulating uncommitted lymphocytes.

The importance of producing cytotoxic immune lymphoid cells is that they have the capacity to traverse capillary beds and carry the immune response into the extra vascular spaces. Non-cytotoxic lymphoid cells are confined to the vascular channels. This is

part of the recognition problem discussed before and indicates the importance of tumor being able to release antigen into the circulation. These in vitro methods may well become of great importance in building up the body's cytotoxic immune lymphocyte population.

2. Increasing the number of sensitised macrophages

Macrophages are sensitised in vivo by the liberation of cytophilic antibody from nearby lymphocytes which coats the surface of the macrophages making them cytotoxic.

Thus the macrophage component could be increased by

(a) Increasing the number of macrophages in the area of a tumor. This can be done by the methods outlined previously for improving the recognition of tumors by macrophages, e.g. causing inflammatory reactions around a tumor bacteria, viruses, chemicals.

or Using injections of macrophage inhibiting factor into a tumor area to localise macrophages in that area. However the various lymphokines have not been purified sufficiently to allow their independent or even amalgamated use.

(b) Theoretically by exposing normal macrophages to spleen cells from immune animals. These cells would release cytophilic antibody to coat the macrophages.

Evans and Alexander have shown that macrophages play the main

part in the rejection of mice ascitic leukaemias.

~~Mathe's~~ Mathe's conclusions from work on mice leukaemias were

- (1) Generally tumor cells are immunotherapeutically more active than BCG
- (2) BCG and tumor cells given together are more active than when each is given alone
- (3) BCG is more active if given in several doses; leukaemic cells are just as active when a single dose is given as when several are given
- (4) Active immunotherapy is effective only when 10^5 leukaemic cells or fewer were grafted

He treated acute lymphoblastic leukaemic patients by first giving them sequential chemotherapy and irradiation to reduce the number of leukaemic cells to a minimum. He then divided his patients at random into four groups

- | | | |
|-----------------------------|---|---|
| (1) no further treatment | - | all relapsed in less than 130 days |
| (2) BCG | } | only 9 out of 20 had relapsed by 130 days |
| (3) leukaemic cells | | |
| (4) BCG and leukaemic cells | | |

There were no significant differences in the rates of relapse in the individual immunotherapy groups.

3. Increasing the amount of cytotoxic antibody

Before discussing methods of doing this the concept of enhancement of tumor growth should be discussed. It is known that injecting an animal with serum from an animal with tumor and then injecting tumor cells into this animal will cause the growth of tumor much more rapidly than if no serum had been given. It is believed that antibody coats the tumor cells and interferes with the recognition process. However note that antibody is given before tumor cells, a situation which does not arise normally.

Immune serum could be raised in animals against tumor cells but the possibility of both cytophilic as well as cytotoxic antibody being present is high and thus the possibility of enhancement would appear to be high. There is also the question of whether the tumor antigens would be strong enough to elicit a tumor specific immune response.

Mathe has shown that enhancing antibodies do exist in patients with choriocarcinoma. However malignant melanoma injections have not been shown to produce enhancing antibodies in the patients affected.

When adequate methods of separating cytotoxic and cytophilic antibodies are found passive immunotherapy, as the technique of raising an immune serum is called, should be useful against tumor cells.

4. The employment of immunological phenomena

(1) Florid Delayed Type hypersensitivity

This method depends on making a tumor more antigenic. Not only does it increase recognition across several fronts, it also allows destruction by a variety of clones of cytotoxic lymphocytes. E. Klein's work on skin tumors was described in some detail under methods of improving recognition. Its effectiveness indicates the potential of this method.

Some of the anti-tumor drugs which act on nucleic acid synthesis may exert part of their effect immunologically due to the alteration in synthesis of some proteins which may be capable of acting antigenically.

(2) Graft v. Host reaction

This reaction occurs when cells of the lymphoid series are grafted from one host to another who is immunologically different. If enough lymphoid cells are grafted or if the host's lymphoid cells are suppressed, then the grafted cells set up immunological reactions

against the host's lymphoid tissue and his other body tissues which are antigenic including any tumor he may have. Injections of immune lymphocytes into immunosuppressed individuals gives a florid graft versus host reaction but although the tumor cells are partially destroyed so are the host cells.

The other approach has been to use specific immune lymphocytes irradiated with 1000r. which allows these cells to retain their anti-tumor activity but stops them from dividing. There is no possibility of a graft versus host reaction but the immune lymphocytes can have an anti-tumor effect on their own. This technique could be used in conjunction with tumor chemotherapy, part of whose theoretically unwanted side effects has been the suppression of the immune system.

In conclusion:

The cell system is there; new antigens exist and the body does react against them but often inadequately. Perhaps we are asking too much of the system to have it work perfectly all the time, to have no inadequacies, no faults. Perhaps our changing environment is bringing about somato genetic change so rapidly that as far as tumors are concerned the defence system cannot cope. It does cope

excellently with homografts and delayed type hypersensitivity, much to our cost at times. However I think the system does have enough potential to make immunotherapy worthwhile in treating tumors although it appears that one must reduce tumor cell mass as much as possible by conventional means before embarking.

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